Mavacamten (CAMZYOS)
National Drug Monograph
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VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information[1]

Description/Mechanism of Action

- Mavacamten is a cardiac myosin inhibitor. Per the product information, in patients with hypertrophic cardiomyopathy (HCM), myosin inhibition with mavacamten reduces dynamic left ventricular outflow tract (LVOT) obstruction and improves cardiac filling pressures.

Indication(s) Under Review in This Document

- Mavacamten is indicated for the treatment of adults with symptomatic New York Heart Association (NYHA) class II-III obstructive HCM to improve functional capacity and symptoms.

Dosage Form(s) Under Review

- Mavacamten is available as 2.5 mg, 5 mg, 10 mg, and 15 mg capsules. The recommended starting dose is 5 mg once daily without regard to food. Subsequent doses with titration are 2.5 mg, 5 mg, 10 mg, or 15 mg once daily. Refer to product information including algorithms for initiation and maintenance for appropriate dosing and monitoring of mavacamten.

REMS

- Use of mavacamten is restricted to the CAMZYOS REMS Program (refer to the product information and VA Specialty Distribution on PBM Sharepoint).

Clinical Evidence Summary[1-3]

Efficacy Considerations

- Approval of mavacamten is based primarily on data from EXPLORER-HCM, a phase 3, randomized, double-blind, placebo-controlled trial in patients with obstructive HCM and NYHA class II to III symptoms.
- Enrollment included patients with a diagnosis of obstructive HCM, defined as unexplained left ventricular hypertrophy with maximal left ventricular wall thickness >= 15 mm (or >= 13 mm if familial HCM); peak LVOT gradient >= 50 mm Hg at rest, after Valsalva maneuver, or post-exercise; left ventricular ejection fraction (LVEF) >= 55%; and NYHA class II to III symptoms. Exclusion criteria included a history of syncope or sustained ventricular tachyarrhythmia with exercise; corrected (Fridericia) QT interval > 500 ms; paroxysmal or intermittent atrial fibrillation; and persistent or permanent atrial fibrillation not on anticoagulation for 4 weeks or more or inadequate rate control. Standard treatment for HCM was allowed to be continued with the exception of disopyramide, or combination of a beta-blocker and a non-dihydropyridine (non-DHP) calcium channel blocker (CCB). Patients were randomized to mavacamten 5 mg once daily or placebo, with dosing individualized to achieve a target reduction in LVOT to less than 30 mm Hg and a mavacamten plasma concentration between 350 to 700 ng/mL. Temporary discontinuation of study drug included a LVEF < 50%.

- The composite primary endpoint to assess clinical response at week 30 compared to baseline was an increase in mixed venous oxygen tension (pVO_2) of 1.5 mL/kg per minute or greater and a reduction of at least one NYHA class; or a 3.0 mL/kg per minute or greater improvement in pVO_2 without worsening of NYHA class. Results showed that 37% of patients treated with mavacamten achieved the primary endpoint compared with 17% of patients in the placebo group (results included in Table 1 below).

Table 1: Primary Endpoint Results (EXPLORER-HCM)[2]

Results	Mavacamten N=123	Placebo N=128	Difference* (95% CI)
Primary endpoint (either of the following)	45 (37%)	22 (17%)	19.4 (8.7 to 30.1) P = 0.0005
>= 1.5 mL/kg/min pVO_2, with >= 1 NYHA class improvement	41 (33%)	18 (14%)	19.3 (9.0 to 29.6)
>= 3.0 mL/kg/min pVO_2, with no worsening NYHA class	29 (24%)	14 (11%)	12.6 (3.4 to 21.9)

CI=Confidence Interval
*model estimated least-square mean difference for continuous variables

- Secondary endpoints included change from baseline in post-exercise LVOT gradient, pVO_2, percent of patients with improvement of at least one NYHA class, and patient-reported outcomes including the Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score (KCCQ-CSS; increase noting improvement) and Hypertrophic Cardiomyopathy Symptom Questionnaire Shortness-of-Breath (HCMSQ-SoB; decrease noting improvement) subscore. These results are presented in Table 2 below.

Table 2: Secondary Endpoint Results (EXPLORER-HCM)[2]

Results	Mavacamten N=123	Placebo N=128	Difference* (95% CI)
Post-exercise LVOT gradient change, mean mm Hg (SD)	-47 (40) N=117	-10 (30) N=122	-35.6 (-43.2 to -28.1) P < 0.0001
Change in pVO_2, mL/kg/min	1.4 (3.1) N=120	-0.1 (3.0) N=125	1.4 (0.6 to 2.1) P = 0.0006
>= 1 NYHA class improvement	80 (65%)	40 (31%)	34% (22 to 45) P < 0.0001
Change in KCCQ-CSS, mean (SD)	13.6 (14.4) N=92	4.2 (13.7) N=88	9.1 (5.5 to 12.7) P < 0.0001
Change in HCMSQ-SoB, mean (SD)	-2.8 (2.7) N=85	-0.9 (2.4) N=86	-1.8 (-2.4 to -1.2) P < 0.0001

CI=Confidence Interval; SD=standard deviation
*model estimated least-square mean difference for continuous variables

- Mean age at baseline was 58.5 years, with 43% of the population from the United States. The majority of patients had NYHA class II symptoms (73%) and were receiving background medical therapy for obstructive HCM, including 75% on a beta-blocker and 17% on a non-DHP CCB at baseline. History of septal reduction therapy was noted in 9% of patients randomized to mavacamten and 6% in the placebo group. Approximately 22% of patients had an implantable cardioverter-defibrillator (ICD) at baseline. Additional baseline parameters were noted for pVO_2 (mavacamten 18.9mL/kg/min, placebo 19.9 mL/kg/min), LVEF (both groups 74%), maximum left ventricular wall thickness (both groups 20 mm), and post-exercise LVOT gradient (mavacamten 86 mm Hg, placebo 84 mm Hg).

Safety Results from Clinical Trials[1-3]

- Per the product information, adverse reactions in > 5% of patients and more commonly on treatment with mavacamten compared to placebo were dizziness (27% vs. 18%, respectively) and syncope (6% vs. 2%,

respectively). It was also noted that syncope was the only adverse drug reaction resulting in discontinuation of therapy with mavacamten (0.8%).

- In EXPLORER-HCM, serious cardiac adverse events occurred in 4 patients on mavacamten (2 atrial fibrillation; 2 stress cardiomyopathy), and 4 in the placebo group (3 atrial fibrillation; 1 atrial fibrillation with congestive heart failure). As noted previously, mean baseline LVEF was 74% in both treatment groups. Over the 30-week treatment period, the mean change from baseline in LVEF was -4% with mavacamten compared to 0% on placebo. During the trial, 7 (6%) patients receiving mavacamten and 2 (2%) patients on placebo experienced a reduction in LVEF to < 50% (median 48%, range 35% to 49%). Five of these patients (3 mavacamten, 2 placebo) had protocol-driven interruption in therapy, with treatment continued after normalization of LVEF. Four patients on mavacamten had LVEF < 50% at 30 weeks (end of the study treatment), which was noted to resolve in 3 of these patients during the 8-week wash-out period. Six patients (3 mavacamten, 3 placebo) who met the predefined criteria for change in corrected QT interval had therapy temporarily interrupted, which was subsequently resumed with the patients completing treatment.
- Adverse events reported with mavacamten in EXPLORER-HCM as noted in the product information are included in Table 3 below.

Table 3: Treatment-Emergent and Serious Adverse Events Reported with Mavacamten[2]

Adverse Events	Mavacamten N=123 (%)	Placebo N=128 (%)
Patients with >= 1 TEAE	108 (88)	101 (79)
Total number SAEs	11	20
Patients with >= 1 SAE	10 (8)	11 (9)
Atrial fibrillation	2 (2)	4 (3)
Syncope	2 (2)	1 (1)
Stress cardiomyopathy	2 (2)	0
Diverticulitis	1 (1)	0
Infection	1 (1)	0
Contusion	1 (1)	0
Forearm fracture	1 (1)	0

SAE=serious adverse event; TEAE= treatment-emergent adverse event

Safety Considerations[1]

- **Boxed warning: Risk of heart failure**
  - Mavacamten reduces LVEF and can cause heart failure due to systolic dysfunction.
  - Echocardiogram assessments of LVEF are required prior to and during treatment with mavacamten. Initiation in patients with LVEF < 55% is not recommended. It is recommended that treatment with mavacamten be interrupted if LVEF is < 50% at any visit or if the patient experiences heart failure symptoms or worsening clinical status.
  - Concomitant use of mavacamten with certain cytochrome P450 inhibitors or discontinuation of certain cytochrome P450 inducers may increase the risk of heart failure due to systolic dysfunction.
  - Due to the risk of heart failure due to systolic dysfunction, mavacamten is available only through the CAMZYOS REMS Program.
- **Contraindications:**
  - Moderate to strong CYP2C19 inhibitors or strong CYP3A4 inhibitors.
  - Moderate to strong CYP2C19 inducers or moderate to strong CYP3A4 inducers.

- **Warnings / precautions**:
    - Heart failure: per the product information, mavacamten reduces systolic contraction and can cause heart failure or totally block ventricular function. Patients who experience a serious intercurrent illness (e.g., serious infection) or arrhythmia (e.g., atrial fibrillation or other uncontrolled tachyarrhythmia) are at greater risk of developing systolic dysfunction and heart failure. It is recommended to assess the patient's clinical status and LVEF prior to and regularly during treatment and adjust the mavacamten dose accordingly. New or worsening arrhythmia, dyspnea, chest pain, fatigue, palpitations, leg edema, or elevations in N-terminal pro-B-type natriuretic peptide (NT-proBNP) may be signs and symptoms of heart failure and should also prompt an evaluation of cardiac function. Asymptomatic LVEF reduction, intercurrent illnesses, and arrhythmias require additional dosing considerations (refer to Dosage and Administration in the product information). Initiation of mavacamten in patients with LVEF < 55% is not recommended. Avoid concomitant use of mavacamten in patients on disopyramide, ranolazine, verapamil with beta-blockers, or diltiazem with beta-blockers as these medications and combinations were excluded from the clinical trial of mavacamten in obstructive HCM (EXPLORER-HCM). Concomitant use of mavacamten with disopyramide in combination with verapamil or diltiazem has been associated with left ventricular systolic dysfunction and heart failure symptoms in patients with obstructive HCM.
    - CYP450 drug interactions leading to heart failure or loss of effectiveness: mavacamten is primarily metabolized by CYP2C19 and CYP3A4 enzymes. Concomitant use of mavacamten and drugs that interact with these enzymes may lead to life-threatening drug interactions such as heart failure or loss of effectiveness. The product information recommends advising patients of the potential for drug interactions, including with over-the-counter medications (such as omeprazole, esomeprazole, or cimetidine). Patients should be advised to inform their healthcare provider of all concomitant products prior to and during treatment with mavacamten.
    - CAMZYOS REMS Program: mavacamten is only available through a restricted program (CAMZYOS REMS Program) because of the risk of heart failure due to systolic dysfunction. Notable requirements of the CAMZYOS REMS Program include the following:
        - Prescribers must be certified by enrolling in the CAMZYOS REMS Program.
        - Patients must enroll in the CAMZYOS REMS Program and comply with ongoing monitoring requirements.
        - Pharmacies must be certified by enrolling in the CAMZYOS REMS Program and must only dispense to patients who are authorized to receive mavacamten.
        - Wholesalers and distributors must only distribute to certified pharmacies.
        - Further information is available at www.CAMZYOSREMS.com or by telephone at 1-833-628-7367.
        - VA prescribers and pharmacies should refer to the VA Specialty Distribution link (PBM Formulary Management - Specialty Distribution Meds - All Documents (sharepoint.com) for information provided in the VA Ordering Summary and Camzyos Patient Prescription Form for VA Patients.
    - Embryo-fetal toxicity: mavacamten may cause fetal toxicity based on animal studies. The product information states to confirm absence of pregnancy in females of reproductive potential prior to treatment and advise patients to use effective contraception during treatment with mavacamten and for 4 months after the last dose. As mavacamten may reduce the effectiveness of combined hormonal contraceptives, it is recommended that patients be advised about this interaction if using combined hormonal contraceptives and to use an alternative contraceptive method that is not affected by CYP450 enzyme induction or to add nonhormonal contraception. It is recommended that females of reproductive potential be advised about the potential risk to the fetus with use of mavacamten during pregnancy.

Other Considerations[1-5]

- Dose titration, maintenance, monitoring, treatment interruption: the product information includes detailed instructions for initiation, maintenance, and interruption of treatment. Initiation or up-titration is not recommended if LVEF < 55%. The recommended starting dose of mavacamten is 5 mg once daily, with monitoring of LVEF and Valsalva LVOT gradient required to appropriately adjust the dose of mavacamten at week 4, week 8, and week 12 (refer to Figure 1 in the product information). During maintenance therapy, the patient's LVEF and Valsalva LVOT gradient are used to adjust the treatment dose as indicated every 12 weeks (refer to Figure 2 in the product information). Instructions for treatment interruption at any clinic visit are also provided if the patient's LVEF is < 50% (refer to Figure 3 in the product information). Per FDA review, it is noted that the more frequent monitoring and slow titration were selected to ensure safe dosing in all patients regardless of CYP2C19 genotype.
- Drug interactions:
    - Mavacamten is primarily metabolized by CYP2C19 and to a lesser extent by CYP3A4 and CYP2C9. As noted above, moderate to strong CYP2C19 inhibitors or strong CYP3A4 inhibitors, as well as moderate to strong CYP2C19 inducers or moderate to strong CYP3A4 inducers are contraindicated in patients being treated with mavacamten.
    - Patients who are on stable therapy with a weak CYP2C19 inhibitor or a moderate CYP3A4 inhibitor may be initiated at the recommended starting dose of mavacamten at 5 mg once daily.
    - It is recommended that the dose of mavacamten be reduced by one level in patients being started on a weak CYP2C19 inhibitor or a moderate CYP3A4 inhibitor. Clinical and echocardiographic assessment should be at 4 weeks, and the dose of mavacamten should not be up-titrated until 12 weeks after initiation of the inhibitor.
    - It is recommended to avoid concomitant initiation of a weak CYP2C19 inhibitor and moderate CYP3A4 inhibitor in patients stable on mavacamten at a dose of 2.5 mg as a lower mavacamten once daily dose is not available.
    - Mavacamten is also an inducer of CYP3A4, CYP2C9, and CYP2C19. It is recommended to closely monitor patients if mavacamten is used in combination with CYP3A4, CYP2C9, or CYP2C19 substrates where reduced plasma concentration may reduce their activity.
    - As progestin and ethinyl estradiol are CY3A4 substrates, concomitant use of mavacamten may lead to contraceptive failure or breakthrough bleeding due to the potential decreased exposure of these hormonal contraceptives. It is recommended to advise patients to use a contraceptive method that is not affected by CYP450 enzyme induction or to add nonhormonal contraception during concomitant use and for 4 months after the last dose of mavacamten.
    - Additive negative inotropic effects may occur when mavacamten is administered with other drugs that reduce cardiac contractility. It is recommended to avoid concomitant mavacamten with disopyramide in combination with verapamil or diltiazem as use has been associated with left ventricular systolic dysfunction and heart failure symptoms.
- Concomitant beta-blockers: a subgroup analysis of whether or not patients were receiving a beta-blocker was performed in patients enrolled in the EXPLORER-HCM trial, noting that most patients not on a beta-blocker were prescribed a non-DHP CCB. Results of the subgroup analysis showed a greater effect in patients not on a beta-blocker (mavacamten N=29, placebo N=33; 52.6%, 95% CI 32.9 to 72.2) compared to those receiving a beta blocker (mavacamten N=94, placebo N=95; 8.7%, 95% CI - 3.6 to 21.1). Mean pVO_2 was lower in patients receiving a beta-blocker at baseline, with a mean change at week 30 that was lower compared to patients not on a beta-blocker. The rate of improvement in NYHA class with mavacamten were similar regardless of the patient receiving treatment with a beta-blocker. In addition, it was noted that all secondary endpoints, including change in LVOT gradient, demonstrated a consistent benefit with mavacamten, regardless of concomitant beta-blocker therapy.
- Patients referred for septal reduction therapy: in a clinical trial (VALOR-HCM) that enrolled 112 patients with obstructive HCM (LVOT gradient >= 50 mm Hg at rest or provocation) with intractable symptoms despite maximal medical therapy (93% NYHA class III/IV, mean post-exercise LVOT gradient 84 +- 35.8 mm Hg) and who met guideline eligibility for septal reduction therapy, treatment with mavacamten demonstrated a reduction in the

primary endpoint (composite of the proportion of patients proceeding with septal reduction therapy or who remained guideline-eligible after 16 weeks of treatment) of 58.9% (95% CI 44.0% to 73.9%) compared to placebo (mavacamten 17.9% vs. placebo 76.8%).

Other Therapeutic Options[1-4]

Mavacamten and other potential pharmacologic therapies for obstructive HCM are listed in Table 4 below.

Table 4: Comparison of Available Agents Used for Obstructive HCM

Treatment	Formulary status	FDA approval	Other Considerations
Mavacamten	NF	Symptomatic NYHA class II-III obstructive HCM to improve functional capacity and symptoms	CAMZYOS REMS Program due to risk of heart failure from systolic dysfunction Boxed warning for risk of heart failure Specific dosing and monitoring recommendations for initiation, maintenance, and interruption of therapy Contraindicated with moderate to strong CYP2C19 inhibitors or strong CYP3A4 inhibitors; moderate to strong CYP2C19 inducers or moderate to strong CYP3A4 inducers Confirm negative pregnancy test prior to prescribing
Beta-blockers (non-vasodilating)	VANF (several agents)	FDA approval for propranolol in HSS; metoprolol off-label use in HCM	AHA/ACC 2020 guideline recommendation (COR: 1; LOE: B-NR): a non-vasodilating beta-blocker as initial pharmacologic therapy for symptomatic obstructive HCM Data with bisoprolol, metoprolol, nadolol (NF), propranolol
Non-DHP CCBs	VANF (diltiazem, verapamil)	Off-label use in HCM	AHA/ACC 2020 guideline recommendation (COR: 1; LOE: verapamil B-NR, diltiazem C-LD): a non-DHP CCB is recommended in patients where a beta-blocker is ineffective or not tolerated
Disopyramide	NF	Off-label use in HCM with LVOTO	AHA/ACC 2020 guideline recommendation (COR: 1; LOE: B-NR): in patients who continue to have severe symptoms despite a beta-blocker or non-DHP CCB, disopyramide in combination with one of the other agents, or septal reduction therapy (performed at an experienced center) is recommended Boxed warning for mortality (refer to prescribing information)

ACC=American College of Cardiology; AHA=American Heart Association; COR=Class of Recommendation (1-Strong); HSS=hypertrophic subaortic stenosis; LOE=Level of Evidence (B-NR moderate quality, nonrandomized; C-LD observation/registry studies, limited data); LVOTO=left ventricular outflow tract obstruction; NF=nonformulary; TBD=to be determined; VANF=VA National Formulary

Projected Place in Therapy[1-5]

- Hypertrophic cardiomyopathy is a genetic disorder, with symptomatic HCM estimated to be less than 1:3,000 adults in the United States. It has been reported that LVOT obstruction (at rest or with provocation) is found in approximately 75% of patients with HCM, with the prevalence of symptomatic obstructive HCM estimated between 2 to 5 per 10,000 patients. Symptoms of obstructive HCM may include dyspnea, fatigue, angina, palpitations, and syncope. Complications of the condition may result in arrhythmias, heart failure, mitral regurgitation, stroke, and sudden cardiac death. Mortality rates related to HCM are reported to be less than 1% per year. Patients at greatest risk for sudden cardiac death may be candidates for ICD placement. Pharmacologic treatment is often considered as initial therapy in patients with symptomatic obstructive HCM, with a non-vasodilating beta-blocker recommended as first line, with titration to symptomatic benefit. A non-DHP CCB

(verapamil or diltiazem) is recommended in patients where a beta-blocker is not effective or not tolerated. In patients with persistent severe symptoms despite a beta-blocker or non-DHP CCB, the addition of disopyramide to one of these therapies is recommended. Septal reduction therapy (surgical myectomy or alcohol septal ablation) may also be considered in patients with persistent severe symptoms despite maximal medical therapy.

- Mavacamten is a cardiac myosin inhibitor indicated for the treatment of symptomatic NYHA class II-III obstructive HCM to improve functional capacity and symptoms. In a randomized clinical trial enrolling 251 patients with symptomatic obstructive HCM, 37% of patients treated with mavacamten achieved the composite primary endpoint compared with 17% of patients in the placebo group. The composite primary endpoint to assess clinical response at week 30 compared to baseline was an increase in pVO_2 of 1.5 mL/kg per minute or greater and a reduction of at least one NYHA class; or a 3.0 mL/kg per minute or greater improvement in pVO_2 without worsening of NYHA class. Secondary endpoints of change from baseline in post-exercise LVOT gradient, pVO_2, percent of patients with improvement of at least one NYHA class, and patient-reported outcomes were significantly improved with mavacamten compared to placebo. Adverse reactions in > 5% of patients and more commonly on treatment with mavacamten compared to placebo were dizziness and syncope. The product information for mavacamten includes a Boxed Warning for risk of heart failure, with treatment available only through the CAMZYOS REMS Program. Mavacamten is contraindicated with moderate to strong CYP2C19 inhibitors or strong CYP3A4 inhibitors, or moderate to strong CYP2C19 inducers or moderate to strong CYP3A4 inducers. Several drug interactions are noted under warnings and precautions, and further described under the drug interactions section of the monograph and the product information. The product information for mavacamten should be consulted for detailed instructions for initiation, maintenance, and interruption of treatment. It is also noted that the product information states to confirm absence of pregnancy in females of reproductive potential prior to treatment and advise patients to use effective contraception during treatment with mavacamten and for 4 months after the last dose, due to the potential risk for embryo-fetal toxicity.
- Place in therapy: Clinical practice guidelines recommend a non-vasodilating beta-blocker as initial pharmacologic therapy for symptomatic obstructive HCM. A non-DHP CCB is recommended in patients where a beta-blocker is ineffective or not tolerated. In patients who continue to have severe symptoms despite a beta-blocker or non-DHP CCB, disopyramide in combination with one of the other agents, or septal reduction therapy (performed at an experienced center) is recommended. Direct comparison trials with mavacamten are currently not available to determine its place in therapy among the agents as recommended above. If it is determined that mavacamten is appropriate for the patient with obstructive HCM, it is noted that the patient and provider are required to be enrolled in the CAMZYOS REMS Program to ensure appropriate dose titration and monitoring, as well as avoidance of drug interactions, due to the potential for reduction in LVEF and risk of heart failure.

References

1. CAMZYOS (mavacamten) capsules for oral use [prescribing information]. Brisbane, CA: MyoKardia, Inc. May 2022.
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5. Desai MY, Owens A, Geske JB, et al. Myosin inhibition in patients with obstructive hypertrophic cardiomyopathy referred for septal reduction therapy. J Am Coll Cardiol 2022;80:95-108.

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